Methodic elaboration for practical lesson in

Dermatovenerology

for students of Medicine Faculty nr.2

Topic N6

Chronic cutaneous Lupus erythematosus
Localized scleroderma (morphea)
Alopecia areata. Vitiligo.

LUPUS ERYTHEMATOSUS

Definition: L.E. is an autoimmune disease of unknown cause involving the skin and/or other organs.

Classification:

l. Chronic cutaneous L E (**CLE)**
2. Sub acute cutaneous L E (**SCLE)**
3. Acute (systemic) L E (**SLE)**

CHRONIC CUTANEOUS LUPUS ERYTHEMATOSUS (CLE)

Epidemiology: Discoid lupus erythematosus (DLE) is responsible for 50-85% of cases of CLE and occurs 2-3 times more frequently in women than in men. DLE is slightly more common in African Americans than in whites or Asians. Although DLE may occur at any age, it most often develops in persons aged 20-40 years.

Pathophysiotogy and etiology: Lupus erythematosus is a polygenic autoimmune disease linked to various HLA subtypes, immune signaling, and environmental factors, which ultimately leads to autoantibody production and T-cell dysfunction. However, the exact etiology of discoid lupus erythematosus (DLE) is not well understood. DLE likely occurs in genetically predisposed individuals, but the exact genetic connection has not been determined. It has been suggested that a heat-shock protein is induced in the keratinocyte following ultraviolet (UV) light exposure or stress, and this protein may act as a target for gamma (delta) T-cell–mediated epidermal cell cytotoxicity. Additionally, toll-like receptors may be involved in the pathogenesis

- Genetic factors: 10 to l2% of patients with LE have at least one family member with this disease. The presence of concordance in 60% of monozygotic twins is another argument for the etiologic role of heredity. There is an evidence for preferential association with certain haplotypes of the major histocompatibility complex (MHC), especially HLA-DR2 and HLA-DR3.
- Ultraviolet light. Exposure to the sun induced skin lesions and can also cause an exacerbation of the disease. UV unregulated cytokines causes release or translocation of sequest ereadntigens and free radical damage.
- Environmental factors: adulterated cooking oil, silica, heavy metals, trichloroethylene, hydrazines, aromatic amines and other chemicals;
- Drugs - hydralazine, procainamide, chlopromazine, sulfonamides, penicillin, isoniazide, anticonvulsivants, minocycline, methyldopa, etc.
- Bacterial and viral factors can provoke and maintain lupus erythematosus lesions.
- Immunologic factors - A wide range of immune abnormalities may contribute to autoantibody production: polyclonal B-cell activation,. molecular mimicry and antibody cross reactivity, loss of T-cell tolerance, abnormal T-cell help, cytokine abnormalities (increased production of IL-I, IL- 4, IL- 6 and IFN gamma) etc.

Auto antibodies can induce tissue damage in LE by two mechanisms:

1. They can bind directly to cells, resulting in type II immunologycally mediated tissue damage;
2. They can bind circulating antigens with formation of immune complexes; leading to type III immunologically mediated tissue damage.

There is also evidence that pro-inflammatory cytokines (TNF, IL-l beta) play an important role in the pathogenesis of LE. Soluble markers of T-cell activation increase in concentration during major exacerbation of the disease.

The expression of vascular, cellular adhesion molecule-l (VCAM-l) is increased in skeletal muscle when LE is associated with per vascular infiltrates

The intercellular adhesion molecule-l (ICAM-1) is increased when these infiltrates are absent. Both types of adhesion molecules are found on intravascular as well as extra vascular cells; hence

during SLE the immune system is activated at many levels. This activation is probably the consequence of changes in the DNA structure

Alterations of coagulation system are also frequent in SLE and results arterial and venous thrombosis. The presence of antiphospholipid antibodies is noted in these cases. Also, plasma from patients with LE enhances platelet aggregation In conclusion, the clotting system is disturbed. LE can be considered as a prototype autoimmune disease.

Clinical features: Chronic cutaneous lupus erythematosus (CLE) can be further divided into 3 main types:

- Discoid lupus erythematosus The most common variant of chronic cutaneous LE, which is named like this, because it's disk-like or coin shape appearance.
- Tumid lupus typically presents with juicy papules and plaques that heal without scarring on the check, on a limb;
- Lupus panniculitis (profundus): infiltration and movable subcutaneous nodule on the submaxillary area, neck, arms, forehead, cheeks, chin, back, buttocks, thighs, scalp, breasts, eyelids etc. Regressed with depression and atrophy by evident scars

The most common variant of chronic cutaneous LE is discoid lupus erythematosus, which is named like this, because it's disk-like or coin shape appearance. It is twice prevalent in women.

The basic symptoms:

- erythema
- follicular hyperkeratosis
- atrophy

Early lesions are usually confined to head and neck and appearing as inflammatory, erythematous, edematous and scaling macules or papules, with few mm in diameter, which spread centrifugally into larger plaques. The scales are adherent, with horny plugs in dilated pilosebaceous canals.

The removal of the scale (s. Besnier-Mescersky) demonstrates a characteristic ,,carpet tack" appearance corresponding to patulous and plugged follicular orifices. The face is most commonly affected. Other sites are: scalp, V area of the neck, ears, dorsum of the hands, rarely arms, legs and trunk. Permanent scarring alopecia occurs in the scalp lesions. Nail changes are subungueal hyperkeratosis, longitudinal striae, and red-blue colorings of the nail plate. Mucous membrane lesions are erythematous patches, hyperkeratotic plaques, leucoplakia and ulcerations, commonly located on the inner cheeks, tongue, lips and palate.

The secondary symptoms:

- pigmetary disturbances (hyperpigmentation and hypopigmentation)
- telangiectasia
- infiltration.

Differential diagnosis: tinea faciei, psoriasis, morphoea, rosacea etc. Associated features: livedo reticularis, erythema multiforme-like lesions, telangiectases, porphyria cutanea tarda, lichen planus et al.

Investigations: Most patients with chronic cutaneous LE remain well. However, screening for SLE and internal disease is still worthwhile.

- A skin biopsy is most helpful if taken from an untreated plaque where appendages are still present. There are vacuolar degeneration of epidermal basal cells, follicular hyperkeratosis, atrophy of the epidermis, papillary dermal edema, a perivascular lymphocytic infiltrate in the dermis and extravasations of erythrocytes.
- Direct immunofluorescence shows deposits of IgG, IgM, IgA and C3 at the basement membrane zone. Biopsies for direct immunofluorescence are best taken from older untreated plaques.
- Blood tests are usually normal but occasionally serum contains antinuclear antibodies

Treatment: Therapy begins with the use of sun-protective measures, including sunscreens, protective clothing, and behavior alteration.

- Standard medical therapy includes antimalarials **(**e.g. hydroxichloroquine) and vitamins group B
- Topical or intralesional corticosteroids
- Topical calcineurin inhibitors
- Topical retinoids

Prognosis: The risk of progression to SLE in patients with DLE was recently demonstrated to be higher than previously reported (16.7% progression within 3 years of diagnosis, as compared with previous data indicating that < 5-10% of patients with DLE progress to SLE). Overall, patients with DLE rarely fulfill 4 or more of the 11 American College of Rheumatology (ACR) criteria used to classify SLE. Serologic abnormalities are uncommon.

MORPHOEA

Localized scleroderma (LS), or morphea, differs from systemic sclerosis (scleroderma) by the presence of various cutaneous morphologic variants and the absence of clinically detectable systemic involvement. There may be overlaps in the pathogenesis of fibrosis in the localized and systemic forms.

Epidemiology

LS has been reported to have an incidence of 2.7 per 100,000. There is a male-female ratio of 1:2 to 3. All variants occur in adults and children and can occur at any age. Linear scleroderma is more common in children and can present in the first or second decade, whereas morphea and generalized morphea are more common in adults and usually present in midlife.

The relative frequency of the different morphologic variants is not clear, and reported studies have found different rates. In affected adults, 35 percent to 65 percent have plaque-type morphea, 8 percent to 9 percent generalized morphea, 6 percent to 46 percent linear scleroderma, 3.5 percent en coup de sabre, 3.5 percent morphea profunda, and less than 1 percent guttate, bullous morphea, and Parry-Romberg syndrome.

The average duration of clinically active disease ranges from 3 to 6 years. In chronic cases, slow clinical progression may persist for decades. Most patients will have a clinical remission of disease.

Etiology and Pathogenesis

The etiology of LS is unknown. There are reports of morphea after infection with measles, varicella, and Borrelia burgdorferi. Other suggested triggers include trauma, bacille Calmette-Guérin vaccination, vitamin B injection, radiation therapy, penicillamine, and bromocriptine. However, no direct etiology has ever been proved. Suggested pathogenic events are similar to those hypothesized for systemic sclerosis. Endothelial cell injury, inflammation and release of cytokines that stimulate collagen production by fibroblasts, and an imbalance of extracellular matrix turnover in the skin seem likely. The reason for the limited distribution of LS is unclear, but the patterning suggests that mosaic genetic changes may contribute.

- Many studies have suggested a pathogenic role for transforming growth factor-β (TGF-β). TGF-β stimulates fibroblasts to produce increased amounts of glycosaminoglycans, fibronectin, and collagen; decreases extracellular matrix breakdown; and it diminishes fibroblast susceptibility to apoptosis. TGF-β has been found to be increased in lesions of LS as well as in the skin and fibrotic lungs of patients with systemic sclerosis. Some work suggests that, at least in systemic sclerosis, TGF-β receptor expression in dermal fibroblasts is increased. There are also data supporting the possibility that alterations in the Smad protein pathway, which is important in TGF-β signal transduction, may play a role in collagen overproduction. Fibroblast cultures derived from systemic sclerosis and LS produce increased amounts of connective tissue components, including collagen type I in vitro. Skin biopsies have shown a greater capacity for collagen overproduction and

sub-population of fibroblasts with activation of type I collagen expression; these fibroblasts co-localize with inflammatory mononuclear cells that express TGF-β. Biopsies of sclerotic lesions also show expression of different isoforms of TGF-β, as well as tissue metalloproteinase-3 (TIMP-3) in sub-populations of fibroblasts cultured from LS lesions. TGF-β enhances TIMP-3 expression, and TIMP-3 inhibits breakdown of collagen. It should be noted that three different isoforms of TGF-β (1, 2, and 3) are present in humans; TGF-β1 is the best studied.

- Some evidence suggests that the fibrotic response may be driven predominantly by $CD4^+$ T cells. Plasma cells and histiocytes can probably contribute to the stimulation of dermal fibroblasts. Inflammatory cells found in the dermis of scleroderma lesions are primarily T lymphocytes, mainly T helper cells. There is also increased interleukin 2 (IL-2) and IL-4 production. At least in the systemic form of scleroderma, connective tissue growth factor has also been implicated.
- A pathogenic role for dermal dendrocytes has also been suggested. The presence of $CD34^+$ and of factor $XIIIa^+$ dermal dendrocytes correlates with active inflammation and sclerosis in LS.
- The pathogenic role of mast cells in LS has not been clearly elucidated, but mast cells may be a component of sclerodermatous skin, especially in the inflammatory and early stages. Mast cell granules contain chemical mediators and proteolytic enzymes that can stimulate fibroblasts and even activate profibrotic cytokines, (i.e., TGF-β); histamine may also stimulate collagen production.

An autoimmune component is supported by the frequent presence of autoantibodies in affected individuals, as well as the association of morphea with other autoimmune diseases, including systemic lupus erythematosus, vitiligo, type 1 diabetes, and autoimmune thyroiditis.

Clinical Findings

There are three main variants of LS: plaque-type morphea, generalized morphea, and linear morphea. Morphea and generalized morphea have a slow and insidious onset and typically affect the trunk. Almost in all clinical forms of localized scleroderma it is possible to note three evolutionary stages: edematous, indurative and atrophic.

- Plaque-type Morphea begins with a patchy, peripherally expanding erythema. As the erythema disappears centrally, a slowly spreading yellow-white lesion evolves. It consists of a firm plate-like plaque that is fixed to the underlying tissue but over which the epidermis can be easily moved. The ivorycolored hardened area is bordered by a blue-pink or violet ring of erythema - the lilac ring. While the sclerotic areas are usually permanent, over many years they can become atrophic. with loss of hair and sweat glands, as well as hypo- and hyperpigmentation.
- Generalized Morphea. is a more severe form of morphea characterized by multiple lesions, when plaque type lesions occur in 3 or more anatomical sites. Commonest sites are the trunk, upper thighs and lumbosacral region. Plaques are oten distributed symmetrically and may become conluent. Plaques at varying stages of evolution usually coexist.
- Linear Morphea. There are two quite distinct variants of this type.
    - Linear scleroderma en Coup de Sabre. The band-like lesion typically extends vertically in a paramedian position from the eyebrows to the scalp, causing scarring alopecia. Occasionally, underlying bone damage or abnormal neurologic findings are seen, Progressive hemifacial atrophy (Parry-Romberg syndrome) is a closely related condition.
    - Linear Morphea of the limbs. The typical patient is young and has a sclerotic band extending down one limb, usually a leg. The sclerosis may interfere with joint motion and limb growth. Such patients often have positive antinuclear antibody findings, in contrast to most other forms of morphea. A “pansclerotic” process involving the entire extremity is seen in very severe cases. Pansclerotic morphea in children has been associated with an increased risk of cutaneous

squamous cell carcinoma, particularly in ulcerated areas of affected skin. Radiologik and electromyographic investigation. may be abnormal.

Other less frequent variants of morphea include supericial (e.g. atrophoderma of Pasini and Pierini), bullous, keloidal, guttate, and subcutaneous morphea.

- **Atrophoderma of Pasini and Pierini** - is uncommon and thought to represent a superficial abortive form of morphea with pigmentary changes, minimal cutaneous induration and superficial reticular dermal change with a benign course. It usually occurs in childhood, with lesions distributed symmetrically on the trunk but it may occur in a zosteriform distribution which follow the lines of Blaschko (atrophoderma of Moulin).
- **Bullous morphea** - his rare subtype is characterized by the presence of tense subepidermal bullae, which appear to develop as a result of subepidermal oedema, and which may occur in the presence of any of the subtypes of morphea. The bullae are most frequent on the legs, and lymphatic dilatation, attributed to obstruction from sclerosis.
- **Keloid Nodular Morphea -** this rare subtype is characterized by the presence of keloid-like nodules in patients with previous or co-existent morphea elsewhere. Lesions are commonest on the upper trunk and may coalesce or occur in a linear pattern.
- **Guttate morphea** - these lesions resemble morphea en plaque, but are smaller (< 1 cm in diameter), and occur on the upper trunk as multiple, faintly erythematous oval lesions, which become yellowish, mildly indurated and which resolve leaving pigmentary changes. Some authors consider this to be a type of lichen sclerosis associated with morphea.
- **Subcutaneous morphea -** The primary site of involvement is the subcutaneous fat, although the fascia may also be involved, making it difficult to distinguish this form from "morphea profunda". The plaques are usually extensive, ill-defined and bounddown, and showed rapid centrifugal progression.

Laboratory abnormalities

Localised scleroderma can usually be recognised by its appearance. The diagnosis can be confirmed by a biopsy. A biopsy is where a small sample of skin is removed under local anaesthetic and examined under the microscope. Sometimes blood tests can give a clue, but there is not a specific blood test for this condition.

- **Histopathology -**The histologic findings of morphea and systemic sclerosis are similar, with a fundamental process of thickening and homogenization of collagen bundles. The depth of involvement is important for categorization into the morphea subtypes. The sclerotic process in superficial circumscribed morphea is centered in the lower reticular dermis, whereas other variants are characterized by replacement of the subcutaneous fat and underlying tissues by collagen. The epidermis is usually normal, but rete ridges may become flattened later in the disease course.
    - In the early inflammatory stage, a perivascular and interstitial variably dense infiltrate of lymphocytes admixed with plasma cells and occasional eosinophils is observed in the reticular dermis and/or the fibrous trabeculae of the subcutaneous tissues. Blood vessel walls demonstrate endothelial swelling and edema, and thickening of preexisting collagen bundles and deposition of fine, wavy fibers of newly formed collagen occur.
    - In the late sclerotic stage, the inflammatory infiltrate typically disappears. Collagen bundles in the reticular dermis and subcutis become thick, closely packed, and hyalinized. Atrophic eccrine glands appear to be trapped within the middle of the thickened dermis as subcutaneous fat is replaced by collagen. A paucity of blood vessels is seen, and adnexal structures are progressively lost. Depending on the subtype, the process of sclerosis may extend into the fascia and even underlying muscle; in contrast, thickened collagen bundles are restricted to the dermis in superficial morphea.
- **Serum Autoantibodies**- have been found with variable frequency in patients with LS.

- The most commonly found autoantibodies are antinuclear antibodies in up to 46 percent to 80 percent of patients, usually with a homogenous immunofluorescence pattern.
- With extensive involvement, 36 percent to 53 percent of cases have anti-single stranded DNA and/or antihistone antibodies.

Typically, patients with generalized morphea have a higher frequency of antibody positivity than other subsets of LS, and autoantibodies correlate with a more severe clinical presentation, greater number of lesions, more sclerotic lesions, and a longer duration of clinical course.

- **Other Serum Abnormalities.**
  - Blood eosinophilia has been described in 6 percent to 50 percent of patients with LS. Levels of eosinophilia appear to correlate with disease activity. Declining levels of eosinophilia may coincide with a decrease in activity of the cutaneous lesions.
  - Elevated immunoglobulins, particularly serum immunoglobulin G levels, have been associated with active, more extensive disease and joint contractures.
  - A positive rheumatoid factor is seen in 26 percent of patients, and the erythrocyte sedimentation rate is elevated in 25 percent.

Treatment

In many cases, LS lesions become inactive spontaneously; however, more severe cases can cause irreversible fibrosis/sclerosis of the skin and subcutaneous tissues. Treatment is directed at the inflammatory component, cytokine release, and activation and collagen deposition. Many therapies have been used in the treatment of LS with variable success.

- Topical and systemic steroids,
- oral (calcitriol), and topical (calcipotriene) vitamin D analogues,
- methotrexat alone or combined with pulsed corticosteroids, cyclophosphamide, azathioprine, hydroxychloroquine, penicillin and D-penicillamine have all been tried
- Mycophenolate mofetil is a second-line agent that has been shown to be effective in patients with MTX-resistant disease.
- topical tacrolimus under occlusion,
- topical imiquimod.
- Other approaches aim to alter the cytokine milieu but await further study. These include topical halofuginone (transforming growth factor-beta synthesis inhibitor), TNF-alpha inhibitors, and thalidomide (interleukin 12 and tumor necrosis factor-alpha inducer).
- Phototherapy may be beneficial as a second-line therapy for refractory or severe disease, or as a first-line therapy for patients with generalized morphea given its low side effect profile compared to immunosuppressive agents.
  - Broadband UVA (320-400 nm, low-dose),
  - Long-wavelength UVA (UVA1; 340-400 nm, low- or medium-dose), and psoralen plus UVA (oral or bath) photochemotherapy has produced marked clinical improvement of morphea lesions in multiple case series and a randomized controlled trial.
  - Narrowband UVB therapy, although less potent owing to its limited dermal penetration, can also be beneficial.

  Regimens combining UV therapy with topical corticosteroids or calcipotriene may be superior to either method alone. A combination of acitretin and PUVA has also shown efficacy.

ALOPECIA AREATA

The lifetime risk of getting alopecia areata is about 2% and, coincidentally, it is the reason for about 2% of consultations in our skin clinics.

Cause

An immunological basis is suspected because of anassociation with autoimmune thyroid disease, vitiligo and atopy. Histologically, T lymphocytes cluster like a swarm of bees around affected hair bulbs, having been attracted and made to divide by cytokines from the dermal papilla. Alopecia areata is probably inherited as a complex genetic trait; sometimes HLA-DQ3, -DR11 or -DR4 act as susceptibility factors, with an increased occurrence in the first-degree relatives of affected subjects and twin concordance.

It affects some 10% of patients with Down's syndrome, suggesting the involvement of genes on chromosome 21. Environmental factors may trigger alopecia areata in the genetically predisposed.

Presentation

Alopecia areata typical patch is uninflamed, with no scaling, but with empty hair follicles. Pathognomonic 'exclamation-mark' hairs may be seen around the edge of enlarging areas. They are broken off about 4 mm from the scalp, and are narrowed and less pigmented proximally. There is present the "shaky hair" sign as a result of thinning of the hair root. Patches are most common in the scalp and beard but other areas, especially the eyelashes and eyebrows, can be affected too. An uncommon diffuse pattern is recognized, with exclamation-mark hairs scattered widely over a diffusely thinned scalp. Alopecia areata can be classified according to its pattern, as follows:

- Reticular - Hair loss is more extensive and the patches coalesce
- Ophiasis - Hair loss is localized to the sides and lower back of the scalp
- Alopecia totalis - 100% hair loss on the scalp
- Alopecia universalis - Complete loss of hair on all hair-bearing areas

Associated conditions may include the following:

- Atopic dermatitis
- Vitiligo
- Thyroid disease
- Collagen-vascular diseases
- Down syndrome
- Psychiatric disorders - Anxiety, personality disorders, depression, and paranoid disorders.
- Stressful life events in the 6 months before onset

Up to 50% of patients show fine pitting or wrinkling of the nails.

Course

The outcome is unpredictable. In a first attack, regrowth is usual within a few months. New hairs appear in the centre of patches as fine pale down, and gradually regain their normal thickness and colour, although the new hair may remain white in older patients. Fifty percent of cases resolve spontaneously without treatment within 1 year, and only 10% go on to have severe chronic disease. Subsequent episodes tend to be more extensive and regrowth is slower. Hair loss in some areas may coexist with regrowth in others. A few of those who go on to have chronic disease lose all the hair from their heads (alopecia totalis) or from the whole skin surface (alopecia universalis). Regrowth is tiresomely erratic but the following uggest a poor prognosis:

1 onset before puberty;

2 association with atopy or Down's syndrome;

3 unusually widespread alopecia; and

4 involvement of the scalp margin (ophiasiform type), especially at the nape of the neck.

Differential diagnosis

Patches are not scaly, in contrast to ringworm, and are usually uninflamed, in contrast to lupus erythematosus and lichen planus. In the hair-pulling habit of children, and in traction alopecia, broken hairs may be seen but true exclamation-mark hairs are absent. Secondary syphilis can also cause a 'moth-eaten' patchy hair loss. A form of scarring alopecia called 'pseudopelade' can look similar. Tinea capitis can be confused this alopecia areata too. But in this case the hair are break down, the skin area is inflamed and covered by scales.

Investigations

None are usually needed. The histology of bald skin shows lymphocytes around and in the hair matrix. Syphilis can be excluded with serological tests if necessary. Organ-specific autoantibody screens provide interesting information but do not affect management.

Treatment

A patient with a first or minor attack can be reassured about the prospects for regrowth.

- The use of *systemic steroids* should be avoided in most cases, but the intradermal injection of 0.2 ml intralesional triamcinolone acetonide (5–10 mg/ml), raising a small bleb within an affected patch, leads to localized tufts of regrowth. While not affecting the overall outcome, this may be useful to re-establish eyebrows or to stimulate hope. It works so reliably that some patients come regularly for reinjections into eyebrows or small areas of the scalp. The downside of this treatment is dermal atrophy evident as depressed areas at the sites of injections.
- *Vitamins* (B5, B6, B8, B9, D3*), amino acids* (cystine and methionine) *and microelements* (e.g. Zinc).
- *Topical corticosteroid creams* of high potency can be prescribed, but it is difficult to tell whether the regrowth is spontaneous or a result of the creams.
- *Mild irritants*, such as 0.1–0.25% dithranol, have been used but with limited success.
- *Ultraviolet radiation* or even psoralen with ultraviolet A (PUVA) therapy may help extensive cases, but hair fall often returns when treatment stops.
- *Contact sensitizers* (e.g. diphencyprone) seemed promising but the long-term effect of persistent antigen stimulation is worrying; they are still being used only in a few centres under trial conditions.
- The efficacy of *topical immunosuppressive agents* (e.g. tacrolimus) has yet to be proved. Wigs are necessary for extensive cases.

DISORDERS OF PIGMENTATION

NORMAL SKIN COLOUR

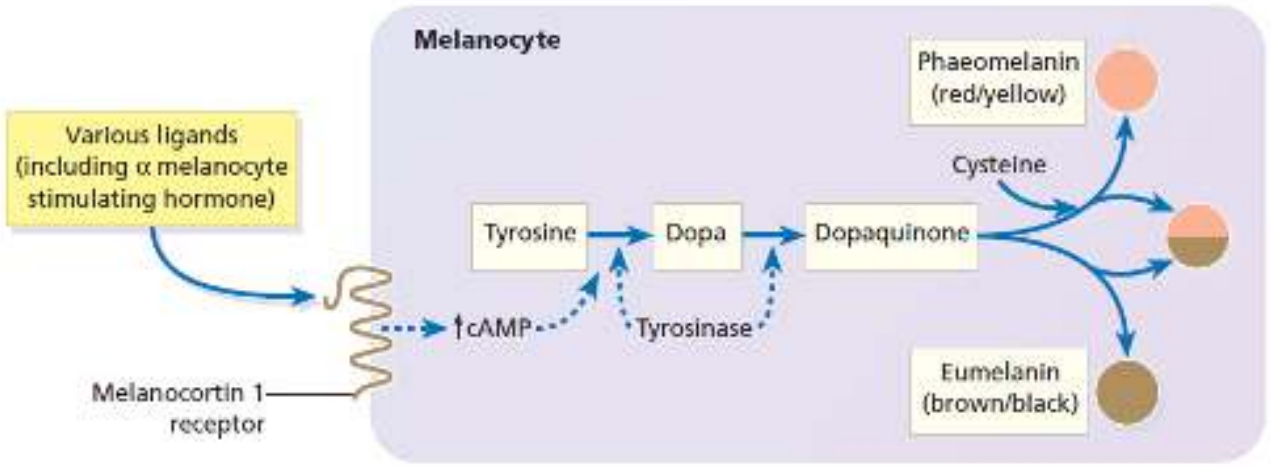
The colour of normal skin comes from a mixture of pigments. Untanned Caucasoid skin is pink, tinted from white by oxyhaemoglobin in the blood within the dermis. Melanin (see below) blends with this colour, and may be increased (e.g. after a suntan). Melanin is also responsible for the shades of brown seen not only in Congoid (Negroid) skin, but also in the other races. Various hues are caused by the addition to these pigments of yellow from carotene, found mainly in subcutaneous fat and in the horny layer of the epidermis. There is no natural blue pigment; when blue is seen, it is either because of an optical effect from normal pigment (usually melanin) in the dermis, or the presence of an abnormal pigment. Skin pigmentation (measured by skin reflectance) is darkest near the equator and correlates with latitude and ultraviolet radiation (UVR). Skin colour seems to have evolved as a compromise between being dark enough to block the damage to DNA caused by ultraviolet radiation and photolysis of the essential metabolite, folate, and light enough to allow vitamin D to be synthesized in the skin.

Hair colour is determined by the relative amounts of the different types of melanin. Eumelanin predominates in black hair and phaeomelanin in red.

MELANOGENESIS

Melanin is formed from the essential aminoacid phenylalanine through a series of enzymatic steps in the liver and skin. Tyrosine, formed in the liver by hydroxylation of the essential amino acid phenylalanine under the influence of phenylalanine hydroxylase, is the substrate for the reactions that occur in melanocytes. These are the only cells in the epidermis to contain tyrosinase (dopa oxidase), the rate-limiting enzyme in melanogenesis. Phaeomelanins and trichochromes, the pigments in red hair, are synthesized in a similar way, except that cysteine reacts with dopaquinone and is incorporated into the subsequent polymers. Phaeomelanins and eumelanins may intermesh to form mixed melanin polymers. Eumelanins and phaeomelanins differ from neuromelanins, the pigments found in the substantia nigra and in cells of the chromaffin system (e.g. adrenal medulla, sympathetic ganglia). The

latter are derived from tyrosine using a different enzyme, tyrosine hydroxylase, which is not found in melanocytes. Melanin is made within melanosomes, tiny particles measuring about 0.1 × 0.7 μm, shaped either like American footballs (eumelanosomes, containing eumelanin) or British soccer balls (phaeomelanosomes, containing phaeomelanin). Eventually, fully melanized melanosomes pass into the dendritic processes of the melanocyte to be injected into neighbouring keratinocytes. Once there, the melanosomes are engulfed in lysosomal packages (melanosome complexes) and distributed throughout the cytoplasm. Such secretory lysosomes are common to various haematopoietic cells and melanocytes. This explains why some genetic disorders of pigmentation (e.g. rare forms of albinism such as the Hermansky–Pudlak and Chediak–Higashi syndromes) are linked with abnormal immune function. Negroids/Congoids are not black because they have more melanocytes than Caucasoids, but because their melanocytes produce more and larger melanosomes, which are broken down less rapidly in the melanosome complexes. Melanins protect against UVR damage by absorbing and scattering the rays, and by scavenging free radicals.



VITILIGO

Background. Vitiligo is a common acquired depigmenting disorder that is characterized by well-demarcated patches of depigmented skin. The cutaneous depigmentation results from the loss of melanocytes in the affected areas. Vitiligo affects approximately I to 3 percent of the population, usually presents by age 40, and shows no racial, sexual, or regional differences.

Etiology. The depigmented lesions of vitiligo are caused by the loss of melanocytes in the skin. The cause of this loss is not known. The three major and potentially overlapping theories that account for vitiligo are intrinsic melanocyted disfunction leading to cell death, a autoimmune-mediated cell destruction, and neurochemical compounds released from nerve endings that have a toxic effect on melartocytes. It seems likely that the bulk of melanocyte destruction in vitiligo is due to the second mechanism: autoimmune destruction. Autoantibodies directed against melanocyte antigens are often present in-pacients sera, and the inflammatory response in depigmented skin is muted. The most frequently associated diseases include thyroid disease, diabetes mellitus, Addisos`s disease, pernicious anemia, and multiple endocrinopathy syndromes. Congenital nevi may be found more commonly in-patients with vitiligo that in the normal population. There seems to be a genetic component predisposing a person to the development of vitiligo.

In addition, many patients note certain precipitating factors. The onset of vitiligo often is attributed to a major emotional stress or severe illness. A significant number of patients also develop lesions of vitiligo at sites of injury or trauma. Exacerbation of disease at sites of trauma is known as Koebner`s phenomenon.

Clinical Presentation. The typical patient presents between ages 10 and 30 years, concerned about the new appearance of white patches on his or her body. The lesions of vitiligo are usually asymptomatic, although patients may complain of being prone to sunburn in affected areas. The lesions of vitiligo are depigmented, milky white macules or patches 1 to 3 cm in size. The borders of

the lesions are usually quite distinct. Often they are distributed on the body in a strikingly symmetric manner, with initial lesions seen commonly on the hands, feet, forearms, anogenital area, face, and lips. Vitiligo may be subclassified in accordance with the distribution of the lesions.

- *Generalized vitiligo,* the most common form, is characterized by varying numbers of widespread macules distributed in a bilateral, symmetric pattern.
- *Universal vitiligo* is the term used when this process leaves only a few remaining normal areas of pigmentation.
- *Acrofacial vitiligo* involves the distal extremities and periorificial facial areas.
- *Focal or localized vitiligo* describes an isolated macule or a few macules in a discrete area.
- *Segmental vitiligo* indicates a situation in which the depigmented macules are localized unilaterally to one area of the body, such as a single extremity.

The clinical course of vitiligo is variable. Some patients have limited disease that is stable, others have progressive disease. The extent of disease may change suddenly. Spontaneous resolution may occur, though not commonly.

Differential diagnosis

- Contact with depigmenting chemicals, such as hydroquinones and substituted phenols in the rubber industry, should be excluded.
- Pityriasis versicolor - yellow-brownish or depigmentated macules, rare erythema and scaling
- Pityriasis alba - scaling, rugous, white or light brown macules localized on the face
- Syphilitic leukomelanodermia - hypopigmented macules surrounded by a hyperpigmented hallo, localized on the neck and upper areas of the trunk
- Post-inflammatory depigmentation may look very like vitiligo but is less white and improves spontaneously.
- The patches of piebaldism are present at birth.
- Sometimes leprosy must be excluded – by sensory testing and a general examination.
- Other tropical diseases that cause patchy hypopigmentation are leishmaniasis and pinta.

Evaluation. The diagnosis of vitiligo generally is based on the clinical findings of depigmented macules in a roughly bilaterally symmetric distribution. Biopsy specimens occasionally is required to common the diagnosis and distinguish vitiligo from other diseases that may be depigmenting, such as lupus erythematous, sarcoidosis, and mycosis fungoides.

Treatment.

- Topical Corticosteroid Agents (midpotency triamcinolone, hydrocortisone valerate, fluticasone) applied twice daily should be the initial therapy in young children, while older children and adults may be started on a high-potency corticosteroid (halobetasol, clobetasol, or betametasone dipropionate) in an optimized vehicle for the first month or two and then tapered to a lower-potency formulation once a response is noted.
- The products which containing genistein (black bean extract), green tea polyphenol, co-enzyme Q10, selenium, alpha-lipoic acid, omega-3 fatty acids, gamma linolenic acid, carotenoids, quercetin, vitamin C, and vitamin E, and others.
- Camouflage Techniques. (eg. Vitiskin)
- Fhototherapy. Psoralen phototherapy (PUVA) - psoralen either orally or topically and then exposing the patient to ultraviolet A (UVA) light (320-400 nm). UVB.